IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Gerard M. Jensen et al.	Art Unit	: 1612
Serial No.	: 10/723,423	Confirm No.	: 6232
Filed	: November 26, 2003	Examiner	: Gollamudi S. Kishore
		Docket	: 01992.005US1
Title	: LIPOSOMAL FORMULATIONS		

REPLY BRIEF

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The Final Office Action for this application was mailed June 24, 2009, and a Notice of Appeal was submitted December 23, 2009. The Examiner submitted an Examiner's Answer on October 21, 2010. By this Reply Brief applicant respectfully appeals to the Board for review of the Examiner's final rejection.

STATUS OF CLAIMS.

The final Office Action mailed June 24, 2009 rejected claims 24-30 and 39-63. No claims have been allowed. Claims 1-53 and 59-63 have been canceled. Therefore, Applicant respectfully appeals the final rejection of claims 54-58.

STATUS OF AMENDMENTS.

Claims 29 and 30 were amended on December 23, 2009, subsequent to the Final Office Action mailed June 24, 2009 to depend from pending claims 54-58.

An Advisory Action was mailed on January 15, 2010, which indicated that the amendments to the claims of December 23, 2009 would not be entered.

Applicant submitted an Amendment After Appeal on July 22, 2010 to cancel claims 1-53 and 59-63. The appealed claims are claims 54-58.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL.

The issues being appealed are the following:

(A) Whether claims 54-58 fail to comply with 35 U.S.C.§112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention; and

(B) Whether claims 54-58 are unpatentable under 35 U.S.C. § 103(a) over the following:

(1) Hersch (US Patent No. 5,759,571, hereinafter "Hersch")) by itself or in combination with Allen (*Biochimica et Biophysica Acta*, 597(1980): 418-426, hereinafter "Allen"), Fujii (US Patent No. 5,328,678, hereinafter "Fujii"), O'Rear (US Patent No. 5,503,850, hereinafter "O'Rear") individually or in combination;

(2) Lopez-Berestein (US Patent No. 5,032,404, hereinafter "Lopez-Berestein") by itself or in combination with Allen, Fujii, and O'Rear, individually or in combination, further in view of Hersch.

(3) Hayes [sic "Hays"] (US Patent No. 5,869,092, hereinafter "Hays") by itself or in combination with Hersch, Allen, Fujii, O'Rear, individually or in combination; and

(4) Hays alone or in combination with Hersch, Allen, Fujii, O'Rear, individually or in combination as set forth above, further in view of Anaissie (US Patent No. 4,999,199, hereinafter "Anaissie").

ARGUMENT

The science of liposomes, including liposomal delivery of therapeutic agents, has been extensively studied. Liposomes can be made from a wide variety of components and the relative amounts of these components can vary widely from system to system. Additionally, the inclusion of therapeutic agents, with inherently different physical properties (*e.g.*, lipophobic agents), within liposomes introduces another source of variability. Thus, the possible number of discreet liposome systems is extremely large.

Certain specific long-circulating liposomes have been studied in human clinical trials. Specification at page 2, lines 9-16. A significant problem with such long-circulating liposomes, however, results from an inability to properly balance the enhanced circulation lifetime of the liposomes with specific drug release profiles. Although investigators have successfully increased the circulation lifetimes of drugs encapsulated in pegylated liposomes, which beneficially promotes accumulation of the liposomes at tumor growth sites, they have been unable to realize acceptable drug release profiles from these liposomes for certain therapeutic agents. Specification at page 2, lines 23-29.

Notwithstanding the significant body of academic and commercial research that has been devoted to liposomal drug delivery and the large body of existing literature that describes this research, at the time of Applicant's discovery there remained a need for liposomal formulations that could be used to deliver non-amphiphilic therapeutic agents at therapeutically useful release rates. Specification at page 3, lines 17-19. Applicant developed such systems, *i.e.*, liposomal systems that provide intermediate elimination half-lives for lipophobic therapeutic agents. Thus, the liposome systems recited in the instant claims can improve the therapeutic index and the activity of the lipophobic agents. Additionally, the drug release profiles for the liposome systems recited in the instant claims are an improvement over the insufficient drug release profiles of the previously available long-circulating liposomes. Thus, the liposome systems recited in the instant claims solve the problem of inadequate drug release encountered in earlier long circulating liposomes. Specification at page 2, lines 28-29. No prior liposome systems provided this combination of useful properties for delivering lipophobic therapeutic agents.

A. Claims 54-58 comply with 35 U.S.C. § 112, second paragraph and are not indefinite.

The Examiner has withdrawn this rejection.

B. Claims 54-58 are patentable over the cited references under 35 U.S.C. § 103(a)

The rejections set forth by the Examiner are as follows:

(1) Rejection of claims 54-58 under 35 U.S.C. § 103(a) as being unpatentable over Hersch (US Patent No. 5,759,571, hereinafter "Hersch")) by itself or in combination with Allen (*Biochimica et Biophysica Acta*, 597(1980): 418-426, hereinafter "Allen"), Fujii (US Patent No. 5,328,678, hereinafter "Fujii"), O'Rear (US Patent No. 5,503,850, hereinafter "O'Rear") individually or in combination

(2) Rejection of claims 54-58 under 35 U.S.C. § 103(a) as being unpatentable over Lopez-Berestein (US Patent No. 5,032,404, hereinafter "Lopez-Berestein") by itself or in combination with Allen, Fujii, and O'Rear, individually or in combination, further in view of Hersch

(3) Rejection of claims 55-56 and 58 under 35 U.S.C. § 103(a) as being unpatentable over Hayes [sic "Hays"] (US Patent No. 5,869,092, hereinafter "Hays") by itself or in combination with Hersch, Allen, Fujii, O'Rear, individually or in combination

(4) Rejection of claim 57 under 35 U.S.C. § 103(a) as being unpatentable over Hayes alone or in combination with Hersch, Allen, Fujii, O'Rear, individually or in combination as set forth above, further in view of Anaissie (US Patent No. 4,999,199, hereinafter "Anaissie")

The Examiner has rejected claims 54-58 as obvious over combinations of seven references. Applicants traverse each of the rejections as well as the responses set forth in the

Examiner's answer with respect to each of the pending claims. Applicant again asserts that the Examiner has not made a legally or factually sufficient *prima facie* case to support an obviousness rejection of claims 54-58 under 35 USC §103(a) and the burden of proving a *prima facie* case remains with the Examiner. Specifically, the Examiner has not shown that the claims which recite specific liposome compositions are obvious over the combinations of seven references relied upon in making the rejections.

In the Appeal Brief, Applicant made specific arguments pertaining to each of the claims in regard to each of the rejections. Respectfully, the Examiner's answer to the Appeal Brief does not overcome those arguments. Applicants specifically reassert each of the arguments made previously in the Appeal Brief.

In making each of the four rejections 35 U.S.C. § 103(a), the Examiner, while citing general principles, does not cite to specific case law. Analysis of relevant case law shows at least two reasons why a *prima facie* case has not been established.

First, the combinations of references fail to establish a *prima facie* case of obviousness. As stated in *Takeda Chemical Industries Ltd. v. Alphapharm Pty., LTD.*, 492 F.3d 1350, 83, USPQ.2d 1356-57 (Fed. Cir. 2007):

> "The test for prima facie obviousness for chemical compounds is consistent with the legal principles enunciated in KSR.... Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound."
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> The Federal Circuit further explained in Takeda that:
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> "We clarified, however, that in order to find a prima facie case of unpatentability in such instances [rejections based upon structural similarity], a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required. Id. (citing In re Jones, 958 F.2d 347 (Fed. Cir. 1992); Dillon, 919 F.2d 688; Grabiak, 769 F.2d 729; In re Lalu, 747 F.2d 703 (Fed. Cir. 1984))."

In the present case, the Examiner has resorted to disclosures from up to five or six references to support each of the rejections. In certain rejections, the Examiner relies upon one reference for disclosure of one liposome component, and upon additional references for

additional liposome components, and for yet another reference to argue that the ratio of the claimed components is disclosed. However, in each case, these rejections do not set forth the way in which the prior art suggests the specific molecular modifications necessary to arrive at the components of the liposomes claimed in claims 54-58 in the ratio specifically claimed. As set forth in Takeda, the knowledge in the cited references that a component may be employed in a certain way or that a particular modification is possible is legally insufficient to sustain a case for obviousness. Therefore, the rejections are legally insufficient to establish a *prima facie* case of obviousness of claims 54-58 for the specific claimed liposomal systems that provide intermediate elimination half-lives for lipophobic therapeutic agents.

Second, the broad range of liposome components disclosed in Hersch is legally insufficient to disclose the range of liposome components specifically claimed in claims 54-58. For example, the Examiner relies on Hersch for disclosure of liposomes comprising HSPC, cholesterol and DSPC. The Examiner asserts that Hersch specifically discloses a ratio of 2:1:0.1. Applicants have previously pointed out that that Hersch does not specifically disclose the ratios set forth in the rejected claims. To make up for this deficiency, the Examiner points to the disclosed range of negatively charged phospholipids is 0 to 20%. Within such a large range, however, it is difficult to see where one of ordinary skill would arrive at the ratio that is set forth in the pending claims. Even within the preferred range of 0 to 5%, the range is too great to disclose the specific range set forth in the present claims. This situation is squarely on point with the situation raised in MPEP§ 2144.05:

> "However, if the reference's disclosed range is so broad as to encompass a very large number of possible distinct compositions, this might present a situation analogous to the obviousness of a species when the prior art broadly discloses a genus. *Id.* See also In re Baird, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); MPEP § 2144.08."

Thus, the range in the Hersch reference cited by the Examiner is so large that it does not fairly disclose the composition of the liposomes in claims 54-58 and the rejections are legally insufficient to establish a prima facie case of obviousness for the specific claimed liposomal systems that provide intermediate elimination half-lives for lipophobic therapeutic agents.

CONCLUSION

Applicant respectfully submits that the Examiner has not met the burden required to establish that claims 54-58 are *prima* facie obvious over the cited documents. Accordingly, withdrawal of the outstanding rejections is appropriate and is respectfully requested.

In light of the remarks provided hereinabove, Applicant believes that the claims are in condition for allowance, and notification to that effect is respectfully requested. If necessary, please charge any additional fees or credit overpayment to Deposit Account 50-3503.

Respectfully submitted,

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Date: 21 December 2010

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